WHAT IS CLAIMED IS:

1. A method of engineering one or more binding macromolecules to adequately bind to a selected target macromolecule, wherein macromolecules comprise linear polymers of monomers, said method comprising:

providing, as a first candidate binding macromolecule, a precursor macromolecule which binds to one or more terminal portions of an initial target macromolecule,

deriving alternative candidate binding macromolecules by replacing one or more monomers of a current candidate with new monomers, wherein the new monomers are selected by rational engineering methods so that the alternative candidates are predicted to bind with one or more terminal portions of the selected target macromolecule, and wherein the rational engineering methods depend on

(i) concerning the selected target macromolecule, input data comprising representations of one or more of its terminal monomer sequences, and

(ii) concerning the precursor macromolecule, input data comprising representations of its monomer sequence and the monomer sequences of one or more of the terminal portions of the initial target macromolecule bound by the precursor,

screening the alternative candidates for new candidates with improved estimated binding to terminal portions of the selected target, wherein the binding is estimated by rational methods in dependence on the input data, and

repeating, if necessary, the steps of deriving and screening until the estimated binding of one or more candidates is adequate, whereby one or more candidate macromolecules are engineered to bind to one or more terminal portions of the selected target macromolecule.

2. The method of claim 1 wherein the input data concerning the precursor macromolecule further comprises representations of its three-dimensional (3D) structure.

3. The method of claim 1 wherein the input data concerning the selected target macromolecule consists essentially of representations of one or more of its terminal monomer sequences.

4. The method of claim 1 further comprising the step of synthesizing one or more of the candidate binding macromolecules having adequate evaluated binding.

5. The method of claim 4 further comprising:

measuring the actual binding of the synthesized candidate macromolecules to the selected target macromolecule, and

repeating, if necessary, the steps of deriving, screening, and repeating and the further steps of synthesizing and measuring, until the measured actual binding of the synthesized candidates is adequate.

6. The method of claim 1 wherein binding is adequate if the dissociation constant (K_d) of a synthesized candidate macromolecule from the selected target macromolecule is less than a preselected maximum value.

7. The method of claim 6 wherein the maximum value is less than approximately 1 mM, or less than approximately 100 μM.

8. The method of claim 1 wherein the rational engineering or estimation methods comprise one or more computer-assisted molecular design (CAMD) methods.

9. The method of claim 1 wherein the steps of deriving and screening are repeated at least twice, wherein the rational engineering or estimating methods used in the later repetitions comprise more accurate methods, and wherein the rational engineering or estimating methods used in the earlier repetitions comprise less accurate methods.

10. The method of claim 1 wherein the monomers are amino acids, and wherein the macromolecules are peptides or polypeptides.

11. A method of engineering one or more binding polypeptides to adequately bind to a selected target polypeptide comprising:

providing, as a first candidate binding polypeptide, a precursor polypeptide which binds to one or more terminal peptide sequences of an initial target polypeptide,

deriving alternative candidate binding polypeptides by replacing one or more amino acid residues of a current candidate with new residues, wherein the new residues are selected by rational engineering methods so that the alternative candidates are predicted to bind with one or more terminal peptide sequences of the selected target polypeptide, and wherein the rational engineering methods depend on

(i) concerning the selected target polypeptide, input data comprising representations of one or more of its terminal peptide sequences, and

(ii) concerning the precursor polypeptide, input data comprising representations of its amino acid sequence, of the amino acid sequences of one or more of the terminal peptide sequences of the initial target polypeptide bound by the precursor,

screening the alternative candidates for new candidates with improved estimated binding to terminal peptide sequences of the selected target, wherein the binding is estimated by rational methods in dependence on the input data, and

repeating, if necessary, the steps of deriving and screening until the estimated binding of one or more candidates is adequate, whereby one or more candidate polypeptides are engineered to bind to one or more terminal peptide sequences of the selected target polypeptide.

12. The method of claim 11 wherein the precursor polypeptide comprises one or more PDZ-type domains, or one or more TPR-type domains, or one or more proline-specific-peptidase-type domains, or one or more class-II-MHC-protein-type domains.

13. The method of claim 11 wherein polypeptides comprise peptides having peptide sequences with lengths of less than approximately 20, or 15, or 10, or 5 residues.

14. The method of claim 13 wherein the one or more terminal peptide sequences of the selected target polypeptide comprise either its N-terminal or its C-terminal peptide sequence, or both.

15. The method of claim 11 wherein the input data concerning the precursor polypeptide further comprises representations of its three-dimensional (3D) structure.

16. The method of claim 11 wherein the input data concerning the selected target polypeptide consists essentially of representations of one or more of its terminal peptide sequences.

17. The method of claim 11 further comprising the step of synthesizing one or more of the candidate binding polypeptides having adequate evaluated binding.

18. The method of claim 17 wherein the step of synthesizing further comprises expression by recombinant genetic engineering methods or synthesis by chemical means.

19. The method of claim 17 wherein the step of synthesizing further comprises synthesizing one or more candidate binding polypeptides fused to one or more other polypeptides.

20. The method of claim 19 wherein the one or more other polypeptides occur in a cell of an organism.

21. The method of claim 19 wherein the one or more other polypeptides comprise green fluorescent protein.

22. The method of claim 17 further comprising:

measuring the actual binding of the synthesized candidate polypeptides to the selected target polypeptide, and

repeating, if necessary, the steps of deriving, screening, and repeating and the further steps of synthesizing, and measuring, until the measured actual binding of the synthesized candidates is adequate.

23. The method of claim 22 wherein the step of measuring further comprises performing affinity chromatography, or biosensor analysis, or micro-calorimetry.

24. The method of claim 22 wherein the step of measuring further comprises performing a yeast two-hybrid assay, or a phage display assay, or RNA-protein fusions.

25. The method of claim 22 further comprising the step of measuring binding specificity by measuring the actual binding of the synthesized candidate polypeptides to a plurality of polypeptides different from the selected target polypeptide.

26. The method of claim 11 wherein binding is adequate if the dissociation constant (K_d) of a synthesized candidate polypeptide from the selected target polypeptide is less than a preselected maximum value.

27. The method of claim 26 wherein the maximum value is less than approximately 1 mM, or less than approximately 100 μM.

28. The method of claim 11 wherein the rational engineering or estimating methods for polypeptides further comprise methods based on by *a priori* chemical or physical principles, or on rules derived from empirical knowledge, or on knowledge in the art.

29. The method of claim 28 further comprising storing information relating to previously engineered binding polypeptides to supplement the empirical knowledge or the knowledge in the art.

30. The method of claim 28 wherein the rational engineering or estimating methods based on principles further comprise one or more computer-assisted molecular design (CAMD) methods for polypeptides.

31. The method of claim 30 wherein the CAMD methods for polypeptides comprise methods which approximate side-chain conformations by rotamers from a rotamer-library, and which approximate polypeptide backbone conformations by an inverse-folding approach in dependence on a known 3D structure.

32. The method of claim 31 wherein the CAMD methods comprises a Perla method.

33. The method of claim 28 wherein the rational engineering or estimating methods based on rules further comprise rules derived from examples of sequence homology with known peptide-sequence-binding polypeptides, or derived from examples of polypeptides that bind to peptide sequences, or derived from examples of chimeric polypeptides formed from known peptide-sequence-binding polypeptides.

34. The method of claim 33 wherein the rules express peptide-sequence-binding specificities of peptide-sequence-binding polypeptides, or wherein the rules express how peptide-sequence-binding specificities of polypeptides may be modified.

35. The method of claim 28 wherein the rational engineering or estimating methods based on common knowledge further comprise rules for classifying amino acids into types with similar physical and chemical properties.

36. The method of claim 11 wherein the steps of deriving and screening are repeated at least twice, wherein the rational engineering or estimating methods used in the later repetitions comprise more accurate methods, and wherein the rational engineering or estimating methods used in the earlier repetitions comprise less accurate methods.

37. The method of claim 11 wherein the precursor polypeptide binds to two or more terminal peptide sequences of the initial target polypeptide, and wherein the step of

repeating, if necessary, repeats the steps of deriving and screening until the estimated binding of one or more candidates to two or more terminal peptide sequences of the selected target polypeptide is adequate.

38. The method of claim 37 wherein the two or more terminal peptide sequences of the selected target polypeptide comprise both the N-terminal and the C-terminal peptide sequences, whereby one or more candidate polypeptides are engineered to bind bivalently to the selected target polypeptide.

39. The method of claim 11 further comprising a step of performing methods of nuclear magnetic resonance spectroscopy or x-ray crystallography to obtain structural data concerning one or more candidates, and wherein the rational engineering and estimating methods further depend on input of this structural data.

40. A method of engineering one or more binding polypeptides to adequately bind to a selected target polypeptide, the method comprising:

providing, as a first candidate binding polypeptide, a precursor polypeptide which binds to one or more N-terminal peptide sequences of an initial target polypeptide, wherein a peptide sequence has a length of less than approximately 20, or 15, or 10, or 5 residues,

deriving alternative candidate binding polypeptides by replacing one or more amino acid residues of a current candidate with new residues,

screening the alternative candidates for new candidates with improved binding to N-terminal peptide sequences of the selected target polypeptide, and

repeating, if necessary, the steps of deriving and screening until the binding of one or more candidates is adequate.

41. The method of claim 40 wherein the precursor polypeptide comprises one or more PDZ-type domains, or one or more TPR-type domains, or one or more proline-specific-peptidase-type domains, or one or more class-II-MHC-protein-type domains.

42. The method of claim 40 wherein the steps of deriving and screening further comprise rational engineering or estimation methods for polypeptides based on by *a priori* chemical or physical principles, or on rules derived from empirical knowledge, or on knowledge in the art.

43. The method of claim 42 wherein the precursor polypeptide has a known three-dimensional (3D) structure.

44. The method of claim 40 wherein the steps of deriving and screening further comprise synthesizing one or more of the alternative candidate binding polypeptides.

45. A computer system for engineering one or more binding polypeptides from a selected precursor polypeptide, wherein the precursor polypeptide binds to one or more terminal peptide sequences of an initial target polypeptide, and wherein the binding polypeptides adequately bind to a selected target polypeptide, the system comprising:

a processor, and

a memory accessible to the processor, wherein the memory is configured with

(a) data for representing the precursor polypeptide, the initial target polypeptide, the selected target polypeptide, and further candidate polypeptides, and wherein

(i) the data for representing the selected target polypeptide comprises data representing one or more of its terminal peptide sequences, and

(ii) the data representing the precursor polypeptide comprises data representing its amino acid sequence and of the amino acid sequences of the one or more terminal peptide sequences of the initial target polypeptide bound by the precursor, and

(b) instructions for causing the processor, in dependence on the represented data, to perform the steps of

(i) rational engineering methods for deriving alternative candidate binding polypeptides by replacing one or more amino acid residues of a current candidate with new residues so that the alternative candidates are predicted to bind with one or more terminal peptide sequences of the selected target polypeptide,

(ii) rational binding-estimating methods for screening the alternative candidates for new candidates with improved estimated binding to terminal peptide sequences of the selected target, and

(iii) repeating, if necessary, the steps of rational engineering and estimating until the estimated binding of one or more candidates is adequate, whereby one or more candidate polypeptides are engineered to bind to one or more terminal peptide sequences of the selected target polypeptide.

46. The system of claim 45 wherein data represents polypeptides as comprising peptides having peptide sequences with lengths of less than approximately 20, or 15, or 10, or 5 residues.

47. The system of claim 45 wherein the data represents one or more terminal peptide sequences of the selected target polypeptide as comprising either its N-terminal or its C-terminal peptide sequence, or both.

48. The system of claim 45 wherein the data representing the precursor polypeptide further comprises data representing its three-dimensional (3D) structure, and wherein the data representing the selected target polypeptide consists essentially of data representing its one or more of its terminal peptide sequences.

49. The system of claim 45 wherein the selected precursor polypeptide binds to two or more terminal peptide sequences of the initial target polypeptide, and wherein the instructions for repeating, if necessary, cause the processor to repeat the steps of rational engineering and rational estimating until the estimated binding of one or more candidates to two or more terminal peptide sequences of the selected target polypeptide is adequate.

50. The method of claim 49 wherein the two or more terminal peptide sequences of the selected target polypeptide comprise both the N-terminal and the C-terminal peptide sequences, whereby one or more candidate polypeptides are engineered to bind bivalently to the selected target polypeptide.

51. The system of claim 45 wherein the instructions for causing the processor to perform the steps of rational engineering or of rational binding-estimating further comprise instructions for performing methods based on by *a priori* chemical or physical principles, or on rules derived from empirical knowledge, or on knowledge in the art.

52. The method of claim 51 wherein the methods based on principles further comprise one or more computer-assisted molecular design (CAMD) methods for polypeptides.

53. The method of claim 52 wherein the CAMD methods for polypeptides comprise methods which approximate side-chain conformations by rotamers from a rotamer-library, and which approximate polypeptide backbone conformations by an inverse-folding approach in dependence on a known 3D structure.

54. The method of claim 53 wherein the CAMD methods comprises a Perla method.

55. The system of claim 52 wherein the instructions for causing the processor to perform a CAMD method further comprise instructions for performing two or more CAMD methods of increasing accuracy.

56. A computer-readable medium with encoded instructions stored therein for causing a computer to perform the method of claim 45.

57. A polypeptide for binding to a selected target polypeptide engineered according to the method of claim 11.

58. A vector for causing expression in a host cell of a polypeptide engineered for binding to a selected target polypeptide according to the method of claim 11.

59. A cell comprising a nucleic acid sequence encoding a polypeptide engineered for binding to a selected target polypeptide according to the method of claim 11.

60. The cell of claim 59 further comprising the engineered polypeptide.

61. The cell of claim 59 further comprising the engineered polypeptide fused to a partner polypeptide comprising a peptide or a polypeptide.

62. The cell of claim 61 wherein the partner polypeptide comprises a polypeptide sequence causing the localization of the fusion to a selected intracellular compartment.

63. The cell of claim 61 wherein the partner polypeptide comprises a polypeptide sequence causing degradation of the fusion.

64. The cell of claim 61 wherein the partner polypeptide comprises a label.

65. The cell of claim 64 wherein the label is green fluorescent protein.

66. A method for altering the function of a first cellular protein, which does not naturally bind to a second cellular protein, comprising:

providing a binding protein engineered according to the method of claim 11 for binding to the second cellular protein, and

expressing the binding protein fused to the first cellular protein so that first cellular protein as part of the fusion binds non-naturally to the second cellular protein.

67. A cell comprising a nucleic acid encoding a cellular protein altered according to claim 66.

68. A method for altering the function of a selected cellular protein, which naturally binds to an initial polypeptide, comprising:

engineering the selected cellular protein to bind to a new target polypeptide according to the method of claim 11, and

expressing the engineered selected cellular protein.

69. The method of claim 68 wherein the initial polypeptide is a part of a first cellular protein to which the selected cellular protein naturally binds, and wherein the new target polypeptide is part of a second cellular protein to which the selected cellular protein does not naturally bind.

70 . The method of claim 68 wherein the selected cellular protein is an enzyme, and wherein the engineered selected protein has altered substrate specificity or enzymatic activity.

71. A cell comprising a cellular protein with function altered according to claim 69.

72. A method for assaying for one or more target polypeptides in a sample comprising:

contacting, in binding conditions, the sample with binding polypeptides, wherein one or more binding polypeptides are engineered by the method of claim 11 to bind to one or more of the target polypeptides, and

assaying for binding polypeptides bound to their respective target polypeptides, whereby the target polypeptides are assayed.

73. The method of claim 72 further comprising, before the step of contacting, a step of attaching one or more binding polypeptides to a substrate.

74. The method of claim 72 wherein the step of assaying further comprises performing affinity chromatography, or biosensor analysis, or nuclear magnetic resonance spectroscopy, or micro-calorimetry.

75. The method of claim 72 wherein the step of assaying further comprises performing a yeast two-hybrid assay, or a phage display assay, or RNA-protein fusion.

76. The method of claim 72 wherein the one or more target polypeptides is a single target polypeptide.

77. A method of determining the cellular localization of a target protein comprising:

providing a binding protein engineered by the method of claim 11 to bind to the target protein,

contacting the cell with the binding protein under binding conditions, and

assaying for the presence and location in the cell of the binding protein bound to the target protein.

78. The method of claim 77 wherein the binding protein is fused to a polypeptide label.

79. The method of claim 77 wherein the step of assaying further comprises performing an immuno-chemical method using antibodies to the binding protein.

80. The method of claim 77 wherein the step of contacting comprises expressing the binding protein in the cell.

81. A method for assaying for target proteins in a sample from an organism comprising:

contacting, in binding conditions, the sample with binding polypeptides, wherein the binding polypeptides bind to one or more terminal peptide sequences of a plurality of selected proteins expressed in the organism, and wherein the plurality of selected expressed proteins comprises more than 50 different proteins, and

assaying for binding polypeptides bound to their respective target proteins, whereby the target proteins are assayed.

82. The method of claim 81 further comprising a step of engineering the binding proteins to bind to the terminal peptide sequences of the selected plurality of proteins by the method of claim 11.

83. The method of claim 81 further comprising the step of expressing the binding proteins in members of one or more libraries of recombinant entities.

84. The method of claim 81 wherein the terminal peptide sequences are N-terminal sequences, or C-terminal sequences, or both, having lengths less than approximately 15 amino acids.

85. The method of claim 81 wherein the plurality of selected proteins comprises more than 500 or more than 5,000 different proteins.

86. The method of claim 81 wherein the plurality of selected proteins comprises less than 5,000 or less than 50,000 different proteins.

87. The method of claim 81 wherein the plurality of selected proteins comprises more than 0.5% of the proteins expressed in a cell of the organism.

88. The method of claim 81 wherein the plurality of selected proteins comprises less than 50% or less than 80% of the proteins expressed in a cell of the organism.

89. The method of claim 81 wherein the binding polypeptides are attached to one or more substrates.

90. A library comprising recombinant organisms expressing a plurality of binding polypeptides,

wherein each binding polypeptide binds to one or more terminal peptide sequences of each of a plurality of selected proteins expressed in an organism, and

wherein the plurality of selected expressed proteins comprises more than 50 different proteins.

91. The library of claim 90 wherein the recombinant organisms comprise phage particles.

92. The library of claim 90 wherein the recombinant organisms are comprise cells for use in a two-hybrid assay.

93. The library of claim 90 wherein the terminal peptide sequences are N-terminal sequences, or C-terminal sequences, or both, having lengths less than approximately 15 amino acids.

94. The library of claim 90 wherein the plurality of selected proteins comprises more than 500 different proteins.

95. The library of claim 90 wherein the plurality of selected proteins comprises more than 5,000 different proteins.

96. The library of claim 90 wherein the plurality of selected proteins comprises less than 5,000 different proteins.

97. The library of claim 90 wherein the plurality of selected proteins comprises less than 50,000 different proteins.

98. The library of claim 90 wherein the plurality of selected proteins comprises more than 0.5% of the proteins expressed in a cell of the organism.

99. The library of claim 90 wherein the plurality of selected proteins comprises less than 50% of the proteins expressed in a cell of the organism.

100. The library of claim 90 wherein the plurality of selected proteins comprises less than 80% of the proteins expressed in a cell of the organism.

101. The library of claim 90 wherein the binding proteins are engineered to bind to the terminal peptide sequences of the selected plurality of proteins by the method of claim 11.

102. A polypeptide array comprising:

a substrate with at least one surface, and

a plurality of binding polypeptides regularly arranged on the surface,

wherein each binding polypeptide binds to one or more terminal peptide sequences of each of a plurality of selected proteins expressed in an organism, and

wherein the plurality of selected expressed proteins comprises more than 50 different proteins.

103. The array of claim 102 wherein the binding polypeptides are covalently attached to the surface.

104. The array of claim 102 wherein the substrate comprises glass or plastic.

105. The array of claim 102 wherein the terminal peptide sequences are N-terminal sequences, or C-terminal sequences, or both, having lengths less than approximately 15 amino acids.

106. The array of claim 102 wherein the plurality of selected proteins comprises more than 500 different proteins.

107. The array of claim 102 wherein the plurality of selected proteins comprises more than 5,000 different proteins.

108. The array of claim 102 wherein the plurality of selected proteins comprises less than 5,000 different proteins.

109. The array of claim 102 wherein the plurality of selected proteins comprises less than 50,000 different proteins.

110. The array of claim 102 wherein the plurality of selected proteins comprises more than 0.5% of the proteins expressed in a cell of the organism.

111. The array of claim 102 wherein the plurality of selected proteins comprises less than 50% of the proteins expressed in a cell of the organism.

112. The array of claim 102 wherein the plurality of selected proteins comprises less than 80% of the proteins expressed in a cell of the organism.

113. The array of claim 102 wherein the binding polypeptides are engineered to bind to the terminal peptide sequences of the selected plurality of proteins by the method of claim 11.

114. A polypeptide-RNA-fusion array comprising:

a substrate with at least one surface, and

a plurality of binding-polypeptide-RNA fusions regularly arranged on the surface,

wherein each binding polypeptide of the fusions binds to one or more terminal peptide sequences of each of a plurality of selected proteins, and

wherein the RNAs of the fusions comprise sequences that encode for the corresponding fused binding polypeptides.

115. The array of claim 114 wherein the terminal peptide sequences are N-terminal sequences, or C-terminal sequences, or both, having lengths less than approximately 15 amino acids.

116. The array of claim 114 wherein the plurality of selected proteins comprises more than 500 different proteins.

117. The array of claim 114 wherein the plurality of selected proteins comprises less than 5,000 different proteins.

118. A method of purifying one or more selected proteins from a sample comprising:

providing one or more binding polypeptides that bind to one or more of the terminal peptide sequences of one or more selected proteins, wherein the binding polypeptides are engineered by the method of claim 11,

contacting the sample in binding conditions with the binding polypeptides so that selected proteins in the contacted sample are bound to the binding proteins,

washing the contacted sample in washing conditions so that unbound proteins are removed while bound selected proteins remain, and

eluting the washed sample in eluting conditions so that bound selected proteins are removed from the binding polypeptides, whereby the eluted selected proteins are purified from the sample.

119. The method of claim 118 wherein the step of providing further provides the binding polypeptides attached to a substrate.

120. The method of claim 118 wherein the steps of contacting, washing, and eluting are performed by the methods of affinity chromatography.

121. The method of claim 118 wherein at least two of the selected proteins are bound in a protein complex.

122. A method of engineering one or more binding macromolecules to adequately bind to a selected target macromolecule, wherein macromolecules comprise linear polymers of monomers, said method comprising:

providing, as a first candidate binding macromolecule, a precursor macromolecule which binds to one or more terminal portions of an initial target macromolecule,

deriving alternative candidate binding macromolecules by replacing one or more monomers of a current candidate with new monomers, wherein the new monomers are selected by rational engineering methods so that the alternative candidates are predicted to bind with one or more terminal portions of the selected target macromolecule, and wherein the rational engineering methods depend on

(i) concerning the selected target macromolecule, input data consisting essentially of representations of one or more of its terminal monomer sequences, and

(ii) concerning the precursor macromolecule, input data comprising representations of its monomer sequence, its three-dimensional (3D) structure, and the monomer sequences of one or more of the terminal portions of the initial target macromolecule bound by the precursor,

screening the alternative candidates for new candidates with improved estimated binding to terminal portions of the selected target, wherein the binding is estimated by rational methods comprising one or more computer-assisted molecular design (CAMD) methods in dependence on the input data, and

repeating, if necessary, the steps of deriving and screening until the estimated binding of one or more candidates is adequate, wherein binding is adequate if the dissociation constant (K_d) of a synthesized candidate polypeptide from the selected target polypeptide is less than approximately 100 μM, whereby one or more candidate macromolecules are engineered to bind to one or more terminal portions of the selected target macromolecule.

123. A method of engineering one or more binding polypeptides to adequately bind to a selected target polypeptide comprising:

providing, as a first candidate binding polypeptide, a precursor polypeptide which binds to one or more terminal peptide sequences of an initial target polypeptide, wherein the one or more terminal peptide sequences of an initial target polypeptide comprise either an N-terminal, or a C-terminal peptide sequence, or both, with lengths of less than approximately 15 residues,

deriving alternative candidate binding polypeptides by replacing one or more amino acid residues of a current candidate with new residues, wherein the new residues are

selected by rational engineering methods so that the alternative candidates are predicted to bind with one or more terminal peptide sequences of the selected target polypeptide, wherein the one or more terminal peptide sequences of the selected target polypeptide comprise either an N-terminal, or a C-terminal peptide sequence, or both, with lengths of less than approximately 15 residues, and wherein the rational engineering methods depend on

(i) concerning the selected target polypeptide, input data consisting essentially of representations of one or more of its terminal peptide sequences, and

(ii) concerning the precursor polypeptide, input data comprising representations of its amino acid sequence, of its three-dimensional (3D) structure, and of the amino acid sequences of one or more of the terminal peptide sequences of the initial target polypeptide bound by the precursor,

screening the alternative candidates for new candidates with improved estimated binding to terminal peptide sequences of the selected target, wherein the binding is estimated by rational methods comprising one or more computer-assisted molecular design (CAMD) methods for polypeptides in dependence on the input data, and

repeating, if necessary, the steps of deriving and screening until the estimated binding of one or more candidates is adequate, wherein binding is adequate if the dissociation constant (K_d) of a synthesized candidate polypeptide from the selected target polypeptide is less than approximately 100 μM, whereby one or more candidate polypeptides are engineered to bind to one or more terminal peptide sequences of the selected target polypeptide.

124. The method of claim 123 wherein the CAMD methods for polypeptides comprise methods which approximate side-chain conformations by rotamers from a rotamer-library, and which approximate polypeptide backbone conformations by an inverse-folding approach in dependence on a known 3D structure.

125. The method of claim 123 wherein the rational engineering or estimating methods further comprise rules derived from examples of sequence homology with known peptide-sequence-binding polypeptides, or derived from examples of polypeptides that bind to peptide sequences, or derived from examples of chimeric polypeptides formed from known peptide-sequence-binding polypeptides.

126. The method of claim 123 wherein the terminal peptide sequences have lengths of less than approximately 10 residues.

127. A method of engineering one or more binding polypeptides to adequately bind to a selected target polypeptide comprising:

providing, as a first candidate binding polypeptide, a precursor polypeptide which binds to two or more terminal peptide sequences of an initial target polypeptide, wherein the two or more terminal peptide sequences of an initial target polypeptide comprise either N-terminal or C-terminal peptide sequences, or both, with lengths of less than approximately 15 residues,

deriving alternative candidate binding polypeptides by replacing one or more amino acid residues of a current candidate with new residues, wherein the new residues are selected by rational engineering methods so that the alternative candidates are predicted to bind with two or more terminal peptide sequences of the selected target polypeptide, wherein the two or more terminal peptide sequences of the selected target polypeptide comprise either N-terminal or C-terminal peptide sequences, or both, with lengths of less than approximately 15 residues, and wherein the rational engineering methods depend on

(i) concerning the selected target polypeptide, input data consisting essentially of representations of two or more of its terminal peptide sequences, and

(ii) concerning the precursor polypeptide, input data comprising representations of its amino acid sequence, of its three-dimensional (3D) structure, and of amino acid sequences of two or more of the terminal peptide sequences of the initial target polypeptide bound by the precursor,

screening the alternative candidates for new candidates with improved estimated binding to terminal peptide sequences of the selected target, wherein the binding is estimated by rational methods comprising one or more computer-assisted molecular design (CAMD) methods for polypeptides in dependence on the input data, and

repeating, if necessary, the steps of deriving and screening until the estimated binding of two or more candidates is adequate, wherein binding is adequate if the dissociation constant (K_d) of a synthesized candidate polypeptide from the selected target polypeptide is less than approximately 100 μM, whereby one or more candidate polypeptides are engineered to bind to one or more terminal peptide sequences of the selected target polypeptide.

128. A computer system for engineering one or more binding polypeptides from a selected precursor polypeptide, wherein the precursor polypeptide binds to one or more terminal peptide sequences of an initial target polypeptide, and wherein the binding polypeptides adequately bind to a selected target polypeptide, the system comprising:

a processor, and

a memory accessible to the processor, wherein the memory is configured with

(a) data for representing the precursor polypeptide, the initial target polypeptide, the selected target polypeptide, and further candidate polypeptides, and wherein

(i) the data for representing the selected target polypeptide consists essentially of data representing one or more of its terminal peptide sequences, wherein the one or more terminal peptide sequences of the selected target polypeptide comprise either an N-terminal, or a C-terminal peptide sequence, or both, with lengths of less than approximately 15 residues, and

(ii) the data representing the precursor polypeptide comprises data representing its amino acid sequence, its three-dimensional (3D) structure, and one or more of the amino acid sequences of the terminal peptide sequences of the initial target polypeptide bound by the precursor, wherein the one or more terminal peptide sequences of the initial target polypeptide comprise either an N-terminal or a C-terminal peptide sequence, or both with lengths of less than approximately 15 residues, and

(b) instructions for causing the processor, in dependence on the represented data, to perform the steps of

(i) rational engineering methods for deriving alternative candidate binding polypeptides by replacing one or more amino acid residues of a current candidate with new residues so that the alternative candidates are predicted to bind with one or more terminal peptide sequences of the selected target polypeptide,

(ii) rational binding-estimating methods comprising one or more computer-assisted molecular design (CAMD) methods for polypeptides for screening the alternative candidates for new candidates with improved estimated binding to terminal peptide sequences of the selected target, and

(iii) repeating, if necessary, the steps of rational engineering and estimating until the estimated binding of one or more candidates is adequate, wherein binding is adequate if the dissociation constant (K_d) of a synthesized candidate polypeptide from the selected target polypeptide is less than approximately 100 μM, whereby one or more candidate polypeptides are engineered to bind to one or more terminal peptide sequences of the selected target polypeptide.

129. The method of claim 128 wherein the terminal peptide sequences have lengths of less than approximately 10 residues.

130 A polypeptide for binding to a selected target polypeptide engineered according to the method of claim 123.

131. A method for assaying for one or more target polypeptides in a sample comprising:

contacting, in binding conditions, the sample with binding polypeptides, wherein one or more binding polypeptides are engineered by the method of claim 123 to bind to one or more of the target polypeptides, and

assaying for binding polypeptides bound to their respective target polypeptides, whereby the target polypeptides are assayed.

132. A polypeptide array comprising:

a substrate with at least one surface, and

a plurality of binding polypeptides regularly arranged on the surface,

wherein each binding polypeptide binds to one or more N-terminal or C-terminal peptide sequences, or both having lengths less than approximately 15 amino acids of each of a plurality of selected proteins expressed in an organism, and

wherein the plurality of selected expressed proteins comprises more than 500 different proteins and less than 50,000 different proteins.

133. A polypeptide array comprising:

a substrate with at least one surface, and

a plurality of binding polypeptides regularly arranged on the surface,

wherein each binding polypeptide binds to one or more N-terminal or C-terminal peptide sequences, or both, having lengths less than approximately 15 amino acids of each of a plurality of selected proteins expressed in an organism, and

wherein the plurality of selected expressed proteins comprises more than 5000 different proteins.